Towards developing meaningful MRI biomarkers of neuroinflammation

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Neuroinflammation is defined as an inflammatory response within the brain or spinal cord. These responses are directed at mitigating external and internal attacks with a combination of responses in order to promote homeostasis. Recently, these processes have become a hot topic in brain research, due to their participation in the pathogenesis of several neurodegenerative and psychiatric disorders (Dheen, Kaur, & Ling, 2007), such as multiple sclerosis, Alzheimer's or Parkinson's disease (Glass, Saijo, Winner, Marchetto, & Gage, 2010; Lassmann, Horssen, & Mahad, 2012). Characterizing the process of neuroinflammation at both acute and chronic stages of neurodegenerative disorder pathogesis is of key importance and can potentially lead to the development of innovative tools for diagnosis and treatment monitoring.

Different cellular subtypes and molecular mechanisms are involved in neuroinflammation, with microglia and astrocytes fulfilling a critical role. Microglia account for approximately 10% of the total cell population in the brain (Lawson, Perry, Dri, & Gordon, 1990). However, based on their monocytic-macrophage lineage origin, they are recognized as the innate immune cells of the central nervous system (Sochocka, Diniz, & Leszek, 2017). Astrocytes, on the other hand, are the most abundant glial cell type in the adult brain (Kettenmann & Ransom, 2005) and contribute to multiple functions, including maintenance of water and ion homeostasis, participation in neurotransmission and contribution to the maintenance of the blood–brain barrier, among others (Kimelberg, 2010; Kimelberg & Nedergaard, 2010). Importantly, inflammation triggers cascades of cellular and molecular events with quite different time courses and spatial distributions. Depending on the inflammatory-agent, for instance, it can be induced an immediate microglia reaction and a delayed astrocyte reaction (reactive astrocytes), or vice versa (Campbell et al., 2012; Gadea, Schinelli, & Gallo, 2008; Jeong, Jou, & Joe, 2010). In this context, it is important to characterize these different patterns or stages in the neuroinflammatory response in order to precisely diagnosis and refine treatments

Animal models of neuroinflammation have been developed to recreate and investigate the different reaction of glia population. A prominent model is the administration of lipopolysaccharide (LPS), a wall component of Gram-negative bacteria, as a neuroinflammation-inducing agent. One effect of LPS is an almost instantaneous induction of microgliosis and a delayed astrogliosis response (Campbell et al., 2012; Jeong et al., 2010). This time course dissociation between microglia and astroglia allows studies in which the contribution of both cell types to the inflammatory process can be disentangled. My work, and the cover image, are related to this time course dissociation and the search of non-invasive biomarkers.

The image on the cover shows a group of reactive astrocytes (Cyan) in the brain of an LPS injected rat. Astrocytes were immunostained using GFAP (Glial Fibrillary Acidic Protein) antibodies, a protein involved in cell migration and motility which label all main processes in these cells (Middeldorp & Hol, 2011). Cell nuclei in the tissue were labeled with DAPI (4',6-diamidino-2-phenylindole), a fluorescent stain that binds to adenine-thymine rich regions in DNA. The picture was taken in the hippocampus. Quantitative analysis of these and other similar images, measuring number, extension and complexity of the ramifications, number of cells and volume for astrocytes, microglia and other cell types, allow us to characterize the effect of LPS and unveil a neuroinflammatory histological fingerprint.

The usefulness of these fingerprints for the study of the pathophysiology of neuroinflammation is clear, however, it is limited to post mortem tissue and, therefore, not applicable in basic longitudinal studies designed to investigate the time course of the pathological process, or clinical setting, where neuroinflammatory biomarkers would have a strong impact in diagnosis and prognosis. In this regard, the overarching goal of my research is to use animal models and histological fingerprints to inform non-invasive magnetic resonance imaging (MRI).

Measures. More specifically, we aim at developing functionalized MRI biomarkers for neuroinflammation, in which a combination of different imaging contrasts could be taken as the fingerprint of the underlying tissue response. The hope is that, by overcoming the lack of specificity in the current MRI imaging techniques, and taking advantage of the animal models to functionalize the biomarkers, we can improve the current diagnostic tools (De Santis & Canals, 2019).